Telomerase governs immunomodulatory properties of mesenchymal stem cells by regulating FAS ligand expression.

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Public Summary:
This study provides the first evidence that TERT regulates the immunomodulatory property of BMMSCs. Elevation of telomerase activity in BMMSCs, as induced by aspirin pretreatment, can improve their immunomodulatory function and reduce their dosage in immune therapy

Scientific Abstract:
Bone marrow mesenchymal stem cells (BMMSCs) are capable of differentiating into multiple cell types and regulating immune cell response. However, the mechanisms that govern the immunomodulatory properties of BMMSCs are still not fully elucidated. Here we show that telomerase-deficient BMMSCs lose their capacity to inhibit T cells and ameliorate the disease phenotype in systemic sclerosis mice. Restoration of telomerase activity by telomerase reverse transcriptase (TERT) transfection in TERT(-/-) BMMSCs rescues their immunomodulatory functions. Mechanistically, we reveal that TERT, combined with beta-catenin and BRG1, serves as a transcriptional complex, which binds the FAS ligand (FASL) promoter to upregulate FASL expression, leading to an elevated immunomodulatory function. To test the translational value of these findings in the context of potential clinical therapy, we used aspirin treatment to upregulate telomerase activity in BMMSCs, and found a significant improvement in the immunomodulatory capacity of BMMSCs. Taken together, these findings identify a previously unrecognized role of TERT in improving the immunomodulatory capacity of BMMSCs, suggesting that aspirin treatment is a practical approach to significantly reduce cell dosage in BMMSC-based immunotherapies.